Sequencing the Therapeutic Options in the Treatment of Multiple Myeloma

Shaji Kumar, M.D.
Professor of Medicine
Chair, Myeloma, Amyloidosis, Dysproteinemia group
Division of Hematology
Mayo Clinic

Scottsdale, Arizona
Rochester, Minnesota
Jacksonville, Florida
Monoclonal gammopathies: a spectrum

Increasing levels of monoclonal protein

Increasing marrow plasma cell percentage

Development of End Organ Damage
Multiple Myeloma (MM)

- Monoclonal proliferation of long lived mature plasma cells.
- Presentation: Include lytic bone disease, hypercalcemia, renal insufficiency, anemia, and infections.

- Accounts for ~ 1.8% of all cancers and ~18% of hematologic malignancies in the US
- ACS estimates 30,770 new myeloma cases in the United States in 2018, with an estimated 12,770 deaths.*

Myeloma Treatment Paradigm

Induction followed by continuous therapy

SCT Eligible

SCT Ineligible

Diagnosis & Risk Stratification

Induction

Consolidation

Maintenance

Relapse

Tumor Burden
Drug Options for MM

• Immunomodulatory drugs
  – *Thalidomide, lenalidomide*

• Proteasome inhibitors
  – *Bortezomib, carfilzomib, ixazomib*

• Traditional chemotherapy
  – *Cyclophosphamide, adriamycin/doxil*

• Monoclonal antibodies
  – *Daratumumab, elotuzumab*
Why care about sequencing?

- Need to treat multiple relapses
- Better understanding of disease biology
- Increasing drug/combination choices: Evidence based using emerging phase 3 data
- Adapting treatment to individual patients: disease heterogeneity
- Need to optimize efficacy, while minimizing toxicity
SWOG S0777: VRd Versus Rd

Randomization
N = 525

Stratification:
• ISS (I, II, III)
• Intent to transplant @ progression (yes/no)

Eight 21-Day Cycles of VRd

Bortezomib 1.3/mg^2 IV
Days 1, 4, 8, and 11
Lenalidomide 25 mg/day PO
Days 1-14
Dexamethasone 20 mg/day PO
Days 1, 2, 4, 5, 8, 9, 11, 12

Lenalidomide 25 mg/day PO Days 1-21
Dexamethasone 40 mg/day PO Days 1, 8, 15, 22

Six 28-Day Cycles of Rd

Lenalidomide 25 mg/day PO
Days 1-21
Dexamethasone 40 mg/day PO
Days 1, 8, 15, 22

ISS, International Staging System; Rd, lenalidomide + dexamethasone; SWOG, Southwest Oncology Group; VRd, bortezomib + lenalidomide + dexamethasone

Durie et al, Lancet 389, 519–527, 4 February 2017
VRd vs. Rd: Survival

Durie et al, Lancet 389, 519–527, 4 February 2017
The estimated 3 year rate of overall survival was 86% in the VTD group and 84% in the TD group ($P=.30$)
## IMF 2013-04 Trial: VTD Versus VCD

<table>
<thead>
<tr>
<th>Intent to treat</th>
<th>VTD (n = 169)</th>
<th>VCD (n = 169)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥CR</td>
<td>13.0%</td>
<td>8.9%</td>
<td>.22</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>66.3%</td>
<td>56.2%</td>
<td>.05</td>
</tr>
<tr>
<td>≥PR</td>
<td>92.3%</td>
<td>83.4%</td>
<td>.01</td>
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</table>

<table>
<thead>
<tr>
<th>Grade 3-4 (%)</th>
<th>VTD (n = 169)</th>
<th>VCD (n = 169)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Any AEs</td>
<td>63.9</td>
<td>68.2</td>
<td>.40</td>
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<tr>
<td>Anemia</td>
<td>4.1</td>
<td>9.5</td>
<td>.05</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18.9</td>
<td>33.1</td>
<td>.003</td>
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<tr>
<td>Infection</td>
<td>7.7</td>
<td>10.1</td>
<td>.45</td>
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<tr>
<td>Thrombocytopenia</td>
<td>4.7</td>
<td>10.6</td>
<td>.04</td>
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<tr>
<td>Thrombosis</td>
<td>1.8</td>
<td>1.8</td>
<td>.99</td>
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<tr>
<td>Cardiac disorders</td>
<td>1.2</td>
<td>0</td>
<td>.16</td>
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<tr>
<td>Cystitis</td>
<td>0</td>
<td>0.6</td>
<td>.32</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>5.3</td>
<td>3.5</td>
<td>.42</td>
</tr>
<tr>
<td>PN</td>
<td>7.7</td>
<td>2.9</td>
<td>.05</td>
</tr>
<tr>
<td>PN grade 2 - 4</td>
<td>21.9</td>
<td>12.9</td>
<td>.008</td>
</tr>
</tbody>
</table>

VTD, bortezomib + thalidomide + dexamethasone; VCD, bortezomib + cyclophosphamide + dexamethasone

Role of ASCT: IFM 2009

VRD 1 cycle

VRD 2 cycles

ASCT

VRD 2 cycles

Stem cell collection

VRD 5 cycles

Len maintenance

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RVD-Alone Group (N=350)</th>
<th>Transplantation Group (N=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response during the study — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>169 (48)</td>
<td>205 (59)</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>101 (29)</td>
<td>102 (29)</td>
</tr>
<tr>
<td>Partial response</td>
<td>70 (20)</td>
<td>37 (11)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>10 (3)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Complete response — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>169 (48)</td>
<td>205 (59)</td>
</tr>
<tr>
<td>Complete response or very good partial response — no. (%)</td>
<td>270 (77)</td>
<td>307 (88)</td>
</tr>
<tr>
<td>Minimal residual disease not detected during the study — no./ total no. with complete or very good partial response (%)‡</td>
<td>171/265 (65)</td>
<td>220/278 (79)</td>
</tr>
</tbody>
</table>
IFM 2009: Survival Outcomes

Progression-Free Survival

Overall Survival

Attal et al, NEJM 2017
What should be done post- ASCT?

• Consolidation with tandem ASCT?

• Non-transplant consolidation?

• Maintenance?
Lenalidomide maintenance

**Graph:**
- **X-axis:** Time (months)
- **Y-axis:** OS (probability)
- **Labels:**
  - Len maintenance: 215/605, Median OS (NR to NR), HR (95% CI) = 0.75 (0.63 to 0.90)
  - Placebo/observation: 275/603, 86.0 months (79.8 to 96.0)

**Box plot:**
- **Variables:** Age (years), Sex, ISS stage, Response after ASCT
- **Comparison:** Len vs Placebo
- **Data Points:**
  - Age (years):
    - ≤ 59: Len = 372, Placebo = 375
    - ≥ 60: Len = 233, Placebo = 228
  - Sex:
    - Male: Len = 322, Placebo = 349
    - Female: Len = 283, Placebo = 254
  - ISS stage:
    - I/II: Len = 411, Placebo = 439
    - III: Len = 113, Placebo = 90
  - Response after ASCT:
    - CR: Len = 65, Placebo = 80
    - CR/VGPR: Len = 314, Placebo = 334
    - PR/SD:
      - Favor Len Maintenance
      - Favor Placebo/Observation

**2017**
Bortezomib maintenance

Progression free survival

Overall survival

<table>
<thead>
<tr>
<th></th>
<th>A: VAD</th>
<th>B: PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/nCR</td>
<td>34</td>
<td>49</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>55</td>
<td>76</td>
</tr>
<tr>
<td>≥PR</td>
<td>83</td>
<td>91</td>
</tr>
</tbody>
</table>

ASH 2010, Abstract #40
EMN02/HO95 MM trial: study design

VMP x 4 cycles
- Bortezomib 1.3 mg/m² d 1,4,8,11,22,25,29,32/42
- Melphalan 9 mg/m² d 1-4/42
- Prednisone 60 mg/m² d 1-4/42
  (497 pts)

Melphalan (HDM) 200 mg/m² x 1-2 courses* + single or double ASCT
  (695 pts)

All pts received lenalidomide maintenance until PD

Stratification: ISS I vs. II vs. III

Randomization to VMP or HDM was 1:1 in centers with a fixed single ASCT policy
Randomization to VMP or HDM-1 or HDM-2 was 1:1:1 in centers with a double ASCT policy
VMP vs. ASCT

Median PFS:
ASCT: NR; VMP: 44.3 mos

HR: 0.76
(95% CI, 0.64-0.90), P=0.002

Number at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>VMP</th>
<th>ASCT</th>
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<tbody>
<tr>
<td>0</td>
<td>497</td>
<td>695</td>
</tr>
<tr>
<td>12</td>
<td>404</td>
<td>597</td>
</tr>
<tr>
<td>24</td>
<td>318</td>
<td>480</td>
</tr>
<tr>
<td>36</td>
<td>201</td>
<td>299</td>
</tr>
<tr>
<td>48</td>
<td>76</td>
<td>110</td>
</tr>
</tbody>
</table>

Cavo et al, ASH 2017
Single versus Tandem ASCT

PFS

OS

HR: 0.71
(95% CI, 0.50-0.98), P=0.040

ASCT-1  ASCT-2

Number at risk
0  12  24  36  48

Cavo et al, ASH 2017
Impact of VRD consolidation

$HR = 0.78 \ (0.61-1.00)$

Sonneveld P et al, Abs 242, ASH 2016
BMT CTN 0702

N=750 pts (250 in each arm)

Register and Randomize → MEL 200mg/m² → Lenalidomide Maintenance **

- Lenalidomide Maintenance **
  - N=257
  - VRD x 4*
    - N=254
    - MEL 200mg/m²
      - N=247

**Lenalidomide x 3 years:
10mg/d for 3 cycles, then 15 mg/d
Every 21 days

* Bortezomib 1.3mg/m2
days 1, 4, 8, 11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg
days 1, 8, 15
Every 21 days

Amendment in 2014 changed Lenalidomide maintenance until disease progression after report of CALGB 100104.
Primary Endpoint: PFS

38 Month Estimate and 95% CI

Auto/Auto: 56.5 (49.4, 62.9)
Auto/RVD: 56.7 (50.0, 62.8)
Auto/Maint: 52.2 (45.4, 58.6)
VISTA trial: MPV vs. MP

San Miguel et al. JCO 2013;31:448-455
RD (continuous or 18 ms) vs. MPT

RVD lite

35-day cycle. Lenalidomide 15 days 1-21; bortezomib 1.3 mg/m2 once weekly subcutaneously days 1, 8, 15, and 22; and dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22 and 23 for pts ≤75 yrs and days 1, 8, 15, 22 for pts older than 75 yrs.

<table>
<thead>
<tr>
<th>Response after 4 cycles (%) (n=30)</th>
<th></th>
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<tbody>
<tr>
<td><strong>ORR (≥PR)</strong></td>
<td>27 (90.0)</td>
</tr>
<tr>
<td>CR</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>VGPR</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>PR</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td><strong>VGPR or better</strong></td>
<td>16 (53.3)</td>
</tr>
</tbody>
</table>

IMWG Criteria; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; VGPR, very good PR.
ALCYONE: Dara-VMP vs. VMP

Key eligibility criteria:
- Transplant-ineligible NDMM
- ECOG 0-2
- Creatinine clearance ≥40 mL/min
- No peripheral neuropathy grade ≥2

1:1 Randomization (N = 706)

VMP × 9 cycles (n = 356)
- Bortezomib: 1.3 mg/m² SC
  - Cycle 1: twice weekly
  - Cycles 2-9: once weekly
- Melphalan: 9 mg/m² PO on Days 1-4
- Prednisone: 60 mg/m² PO on Days 1-4

D-VMP × 9 cycles (n = 350)
- Daratumumab: 16 mg/kg IV
  - Cycle 1: once weekly
  - Cycles 2-9: every 3 weeks
- Same VMP schedule

Follow-up for PD and survival

Primary endpoint:
- PFS

Secondary endpoints:
- ORR
- ≥VGPR rate
- ≥CR rate
- MRD (NGS; 10⁻⁵)
- OS
- Safety

Stratification factors
- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

D Cycles 10+
- 16 mg/kg IV
- Every 4 weeks: until PD

Statistical analyses
- 360 PFS events: 85% power for 8-month PFS improvement
- Interim analysis: ~216 PFS events

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; EU, European Union; SC, subcutaneously; PO, orally; D, daratumumab; IV, intravenously; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; NGS, next-generation sequencing; OS, overall survival.

*8-month PFS improvement over 21-month median PFS of VMP.

Mateos et al, ASH 2017
ALCYONE: Dara-VMP vs. VMP

• Median (range) follow-up: 16.5 (0.1-28.1) months

50% reduction in the risk of progression or death in patients receiving D-VMP

HR, 0.50
(95% CI, 0.38-0.65; P <0.0001)

HR, hazard ratio; CI, confidence interval.
+aKaplan-Meier estimate.
Continuous therapy vs. fixed duration

**Progression-Free Survival (probability)**

- CT: 417, 219, 9
- FDT: 410, 308, 13

HR: 0.47; 95% CI: 0.40 to 0.56; \( P < 0.001 \)

**Overall Survival (probability)**

- CT: 417, 111
- FDT: 410, 143

HR: 0.65; 95% CI: 0.54 to 0.88; \( P = 0.003 \)
Relapsed MM: Scope of the problem

- Median time to first relapse with current therapies: 3-4 years
Development of resistance

Kumar et al, unpublished data; Lohr et al, Cancer Cell 25 (1), 2014, 91–101
Clonal selection by therapy

- 5 unique clones at diagnosis
- Variable chemotherapy response
- Minor drug resistant clone lethal

Keats et al, Blood
General principles

• Duration of initial response defines biology

• Triplet (two active classes + dex) preferred over doublet
  – At least one drug from a non-refractory class

• Consider PS, age and comorbidities when selecting drug/doses

• Take into account prior toxicities/residual toxicities

• Treat to maximum response and maintain on one drug till progression or tolerability
The landscape of relapsed MM

VRD / VCD

With or without Break

VRD / VCD

SCT

Len / Btz Maintenance

First Relapse

RD

With or without Break
Not refractory to bortezomib
Carfilzomib-Dexamethasone

- Twice weekly infusion
- High rates of cardiovascular and renal toxicity

Dimopoulos et al, Lancet 2016
PANORAMA: Panobinostat-Btz D

- Twice weekly infusion
- High rates of cardiovascular and renal toxicity

**PFS 12 vs. 8 months**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>61%</td>
</tr>
<tr>
<td>&gt;=VGPR</td>
<td>28%</td>
</tr>
<tr>
<td>&gt;=CR</td>
<td>11%</td>
</tr>
</tbody>
</table>

San Miguel et al, Lancet Oncology, 2014, 5(11), 1195–1206
Daratumumab bortezomib Dex

- Twice weekly infusion
- High rates of cardiovascular and renal toxicity

Median progression-free survival:
- Daratumumab Group (N=251): NE
- Control Group (N=247): 7.2

ORR 83%
>=VGPR 59%
>=CR 19%

Hazard ratio for progression or death, daratumumab vs. control, 0.39 (95% CI, 0.28–0.53), P<0.001

Elotuzumab-Bortezomib-Dex

<table>
<thead>
<tr>
<th></th>
<th>EBd (events: 52/77)</th>
<th>Bd (events: 59/75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year PFS</td>
<td>39%</td>
<td>33%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>9.7 months (7.4-12.2)</td>
<td>6.9 months (5.1-10.2)</td>
</tr>
<tr>
<td>HR</td>
<td>0.72 (70% CI, 0.59-0.88; 95% CI, 0.49-1.06); stratified log-rank P = .09</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>EBd (events: 17/77)</th>
<th>Bd (events: 23/75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year OS</td>
<td>85%</td>
<td>74%</td>
</tr>
<tr>
<td>HR</td>
<td>0.61 (95% CI, 0.32-1.15; 70% CI, 0.43-0.85)</td>
<td></td>
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</table>
Randomized trial of Btz-Dex combinations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Control</th>
<th>N</th>
<th>&gt;=PR</th>
<th>&gt;=VGPR</th>
<th>&gt;=CR</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endeavor</td>
<td>Cfz-Dex</td>
<td>Btz-Dex</td>
<td>464</td>
<td>76</td>
<td>54</td>
<td>13</td>
<td>18.7 (vs. 9.4)</td>
</tr>
<tr>
<td>Panorama</td>
<td>Pano-Btz-Dex</td>
<td>Btz-Dex</td>
<td>387</td>
<td>61</td>
<td>28</td>
<td>11</td>
<td>12 (vs. 8)</td>
</tr>
<tr>
<td>Castor</td>
<td>Dara-Btz-Dex</td>
<td>Btz-Dex</td>
<td>251</td>
<td>83</td>
<td>59</td>
<td>19</td>
<td>NR (vs. 7.2)</td>
</tr>
<tr>
<td>Randomized Phase 2</td>
<td>Elo-Btz-Dex</td>
<td>Btz-Dex</td>
<td>77</td>
<td>67</td>
<td>37</td>
<td>4</td>
<td>9.7 (vs. 6.9)</td>
</tr>
</tbody>
</table>
Not refractory to lenalidomide
ASPIRE: Carfilzomib-Rd

- Two infusions per week for 3/4 weeks
- Well tolerated

Stewart et al, NEJM 2015
Tourmaline: Ixazomib-Rd

- All oral regimen
- Well tolerated

ELOQUENT: Elotuzumab-Rd

- One infusion every other week
- Well tolerated

HR 0.73 (95% CI 0.60, 0.89); p=0.0014

Median PFS (95% CI)
19.4 mos (16.6, 22.2)
14.9 mos (12.1, 17.2)

ORR 79%
>VGPR 33%
>CR 4%
Daratumumab-Rd (Pollux)

- One infusion weekly for 8, every other week for 8, then monthly
- Well tolerated, infusion reactions cycle 1

ORR 87%
>=VGPR 70%
>=CR 32%
Randomized trials of Len-Dex combinations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Control</th>
<th>N</th>
<th>&gt;=PR</th>
<th>&gt;=VGPR</th>
<th>&gt;=CR</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspire</td>
<td>Cfx-Len-Dex</td>
<td>Len-Dex</td>
<td>207</td>
<td>87</td>
<td>70</td>
<td>32</td>
<td>26.3 (vs. 17.6)</td>
</tr>
<tr>
<td>Tourmaline</td>
<td>Ixa-Len-Dex</td>
<td>Len-Dex</td>
<td>360</td>
<td>78</td>
<td>48</td>
<td>12</td>
<td>20.6 (vs. 14.7)</td>
</tr>
<tr>
<td>Pollux</td>
<td>Dara-Len-Dex</td>
<td>Len-Dex</td>
<td>286</td>
<td>87</td>
<td>70</td>
<td>32</td>
<td>NR (vs. 7.2)</td>
</tr>
<tr>
<td>Eloquent</td>
<td>Elo-Len-Dex</td>
<td>Len-Dex</td>
<td>299</td>
<td>79</td>
<td>33</td>
<td>4</td>
<td>19.4 (vs. 14.9)</td>
</tr>
</tbody>
</table>
Not refractory to lenalidomide OR bortezomib
Many options

- Consider bortezomib, lenalidomide, dex (VRd)
- Repeat induction regimen
- Any of the triplets studied above
- VCD is another choice
Refractory to lenalidomide AND bortezomib
Changing the drug class

**OS**

- **Dara**: HR = 0.44 (95% CI 0.31–0.63)
- **Standard of care**

**PFS**

- **Dara**: HR = 0.56 (95% CI 0.42–0.74)

Kumar et al, ASH 2016
### Daratumumab

<table>
<thead>
<tr>
<th>Overall response rate (sCR+CR+VGPR+PR)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>0</td>
</tr>
<tr>
<td>VGPR</td>
<td>1%</td>
</tr>
<tr>
<td>CR</td>
<td>2%</td>
</tr>
<tr>
<td>MR</td>
<td>18%</td>
</tr>
<tr>
<td>ORR = 31%</td>
<td></td>
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<table>
<thead>
<tr>
<th>Best response</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>sCR</td>
<td>3 (2)</td>
</tr>
<tr>
<td>CR</td>
<td>2 (1)</td>
</tr>
<tr>
<td>VGPR</td>
<td>14 (10)</td>
</tr>
<tr>
<td>PR</td>
<td>27 (18)</td>
</tr>
<tr>
<td>MR</td>
<td>9 (6)</td>
</tr>
</tbody>
</table>

| VGPR or better (sCR+CR+VGPR)       | 19 (13) |
| CR or better (sCR+CR)              | 5 (3)   |

[Diagram showing ORR = 31%]

Usmani et al, Blood 2016
Carfilzomib, pomalidomide, Dex

Shah, J et al, Blood 2015 126:2284-2290
Daratumumab, pomalidomide, dex

<table>
<thead>
<tr>
<th></th>
<th>DARA + POM-D (N = 75)</th>
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<tbody>
<tr>
<td>Overall response rate</td>
<td>n (%) 95% CI</td>
</tr>
<tr>
<td>(sCR+CR+VGPR+PR)</td>
<td>53 (71) 59.0-80.6</td>
</tr>
<tr>
<td>Best response</td>
<td></td>
</tr>
<tr>
<td>sCR</td>
<td>4 (5) 1.5-13.1</td>
</tr>
<tr>
<td>CR</td>
<td>3 (4) 0.8-11.2</td>
</tr>
<tr>
<td>VGPR</td>
<td>25 (33) 22.9-45.2</td>
</tr>
<tr>
<td>PR</td>
<td>21 (28) 18.2-39.6</td>
</tr>
<tr>
<td>MR</td>
<td>2 (3) 0.3-9.3</td>
</tr>
<tr>
<td>SD</td>
<td>17 (23) 13.8-33.8</td>
</tr>
<tr>
<td>PD</td>
<td>3 (4) 0.8-11.2</td>
</tr>
<tr>
<td>VGPR or better (sCR+CR+VGPR)</td>
<td>32 (43) 31.3-54.6</td>
</tr>
<tr>
<td>CR or better (sCR+CR)</td>
<td>7 (9) 3.8-18.3</td>
</tr>
</tbody>
</table>

ORR = 71%

CR or better (sCR+CR) 28%
VGPR or better 33%

9% CR or better

N = 75

Chari, Aet al, ASH 2015
Salvage HDT

B. Progression-free survival

C. Overall survival

Cook et al., 15 (8), July 2014, 874–885
Chemotherapy drugs

- Alkylators (*Melphalan, cyclophosphamide, bendamustine*)
- Anthracycline
- Cisplatin
- Etoposide
- BCNU
Second and Higher Relapse
A possible approach

Not refractory to Len at 1st relapse

KRd → DRd → DPd

IRd → ERd → KPd → DPd

Not refractory to Btz at 1st relapse

KD → DVd → DPd

EVd

Clinical trials OR Repeat combinations of agents most remotely used

Overall: while triplets are preferred, lower dose triplets or doublets can be used in frail and older patients
Relapsed, refractory disease: New Agents
Selinexor

- Exportin 1 (XPO1) is the nuclear exporter for the majority of tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR), and eIF4E-bound oncoprotein mRNAs

- Selinexor is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression
## Selinexor: Efficacy

<table>
<thead>
<tr>
<th>Category</th>
<th>N*</th>
<th>ORR (%)</th>
<th>CBR (%)</th>
<th>VGPR (%)</th>
<th>PR (%)</th>
<th>MR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>78</td>
<td>16 (21%)</td>
<td>26 (33%)</td>
<td>4 (5%)</td>
<td>12 (15%)</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>Quad Refractory</td>
<td>48</td>
<td>10 (21%)</td>
<td>14 (29%)</td>
<td>2 (4%)</td>
<td>8 (17%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Penta Refractory</td>
<td>30</td>
<td>6 (20%)</td>
<td>12 (40%)</td>
<td>2 (7%)</td>
<td>4 (13%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>6 Doses / Month</td>
<td>51</td>
<td>10 (20%)</td>
<td>15 (29%)</td>
<td>3 (6%)</td>
<td>7 (14%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>8 Doses / Month</td>
<td>27</td>
<td>6 (22%)</td>
<td>11 (41%)</td>
<td>1 (4%)</td>
<td>5 (19%)</td>
<td>5 (19%)</td>
</tr>
</tbody>
</table>

Vogl et al, ASH 2016
Venetoclax

- Venetoclax induces cell death in multiple myeloma (MM) cell lines and primary samples, particularly those positive for the translocation t(11;14), which correlates with higher ratios of BCL2 to MCL1 and BCL2 to BCL2L1 (BCL-XL) mRNA\(^1,2\)

Venetoclax: Efficacy

Kumar et al, ASH 2016
CAR T-cell Approach

- **Ectodomain (antigen recognition)**
  - Linker
  - Light (or heavy) chain
    - Derived from an scFv of known specificity
  - Heavy (or light) chain
    - Derived from CD8 or IgG4
  - Hinge region
    - Derived from the transmembrane domain of CD8 or CD28
- **Lipid bilayer**
- **Transmembrane domain**
- **Endodomain (stimulation)**
  - **Co-stimulatory molecule(s)**
    - None, one, or more of: CD27, CD28, ICOS, 4-1BB, OX40
  - **Stimulatory molecule**
    - CD3ζ, chain or Fcγ chain

Clinical results: BCMA CART

Conclusions

• Therapeutic advances have led to prolonged survival in MM, but remains a chronic disease
• Treatment of myeloma requires a long term strategy
• Key is delivering the best ‘package’ of treatment at a given stage
• Optimal combinations and sequencing is key
• Risk stratified approach in clinic
• Future will be developing more individualized approaches